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Neurochemistry of Brain Lesions Determined by Spectroscopic Imaging in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** The significance and etiology of focal brain lesions in systemic lupus erythematosus (SLE) are unknown. Our purpose was to determine whether the neurochemistry of focal lesions and normal appearing brain tissues in SLE were consistent with neuronal loss, demyelination, or ischemia.

Methods. Patients with SLE (n = 14) and controls (n = 13) were studied using magnetic resonance imaging (MRI) and spectroscopic imaging (SI) at 1.5 Tesla.

Results. MRI detected fixed focal brain lesions (n = 16) and SI measured brain metabolites, including N-acetylaspartate (NAA), creatine (Cre), choline (Cho), and lactate (Lac). NAA/Cre of normal appearing brain was decreased in patients with SLE compared to controls: grey matter (1.74 ± 0.16 vs 1.92 ± 0.18; p = 0.01), occipital white matter (1.98 ± 0.22 vs 2.23 ± 0.16; p = 0.004), and periventricular white matter (2.00 ± 0.23 vs 2.33 ± 0.23; p = 0.001). Lesions were characterized by markedly decreased NAA/Cre relative to normal appearing tissues in the same patient (1.67 ± 0.22 vs 1.88 ± 0.14; p = 0.0002). Elevated Cho/Cre was observed in 25% of focal lesions and 21% of normal appearing tissues. No elevation of lactate was observed in lesions or normal appearing tissues.

Conclusion. SI detects focal and generalized brain abnormalities in SLE characterized by decreased NAA, elevated choline, and normal lactate. These findings are consistent with widespread neuronal injury and demyelination, but are not consistent with anaerobic metabolism. (*J Rheumatol 1997;* **24:2323–9**)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS SPECTROSCOPY
NUCLEAR MAGNETIC RESONANCE NEUROCHEMISTRY BRAIN INJURIES

Neuropsychiatric systemic lupus erythematosus (NPSLE) is a serious complication of SLE that affects as many as 75% of patients[1,2]. Manifestations include headache, psychiatric disturbances, affective disorders, cognitive dysfunction, cerebrovascular accidents, transverse myelitis, movement disorders, seizures, and aseptic meningitis[3–5].

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Magnetic resonance imaging (MRI) is frequently employed to evaluate NPSLE, revealing diffuse periventricular hyperintensities, infarcts, hemorrhage, cerebral atrophy, or small focal lesions[6–8]. Both reversible and irreversible focal lesions have been reported[9]. Although irreversible focal lesions may represent infarct, large scale paired MRI–autopsy studies to confirm this association are lacking[10]. We reported that NPSLE is characterized by loss of the neuronal marker N-acetylaspartate (NAA), suggesting diffuse neuronal loss[11,12]. The spin-spin (T2) relaxation characteristics of cerebral infarct, reversible focal lesions, and fixed focal lesions in NPSLE are different, indicating different micropathology and biochemical microenvironments[13]. We hypothesize that irreversible focal lesions on T2 weighted MR images in NPSLE represent focal neuronal injury in various stages of evolution. We address this hypothesis by determining the neurochemistry of brain lesions and normal tissues using magnetic resonance spectroscopic imaging (SI).

MATERIALS AND METHODS

Subjects. Fourteen patients with SLE (mean age 34 ± 4 yrs; range 21 to 46) and 13 controls (mean age 33 ± 3 yrs; range 22 to 44) (p > 0.35) were studied. SLE was diagnosed according to the 1982 revised criteria of the

American College of Rheumatology[14]. The presence of NPSLE was determined using the method of Carbotte, *et al*[15]. Seven patients were receiving low dose corticosteroids (prednisone 5–20 mg/day). Table 1 summarizes patient data. Since the object of this study was to characterize fixed (irreversible) focal lesions, patients with active major NPSLE (active or recent seizures, psychosis, encephalopathy, coma, stroke, focal neurologic deficit) were excluded, since focal lesions associated with active major NPSLE may be reversible[13]. "Fixed focal lesions" were defined as hyperintense focal lesions that could be identified on 2 successive T2 weighted MRI examinations performed at least 4 months apart. Because the spectroscopic method defined volumes of interest as 1 ml voxels, only focal white matter hyperintensities on T2 weighted MR images that were large enough to fill 1 voxel (7 mm diameter lesion on 15 mm thick images) were studied. This criterion minimized partial volume effects created by the unintentional inclusion of nonlesional tissue in the spectroscopic voxel. A total of 16 fixed focal lesions were analyzed by SI. Patients with lesions that fit the above criteria were classified as "SLE with lesion" ($n = 6$) and those who did not as "SLE without lesion" ($n = 8$). None of the healthy controls had lesions.

Data acquisition. Data were acquired at 1.5 Tesla with a clinical scanner (GE Medical Systems, Waukesha, WI, USA) using a head coil for transmission of radiofrequency pulses and detection of signals. Sagittal T1 weighted images (TE = 16 ms; TR = 600 ms) were used to select 3 slices aligned parallel to the anterior-posterior commissural line for spectroscopic imaging. Oblique-axial proton density/T2 weighted MR images (TE = 30/100 ms; TR = 2800 ms; FOV = 20 cm; 15 mm slice thickness; 2.5 mm gap) coinciding with the selected locations of the spectroscopic images were obtained. SI was performed with TE = 270 ms, TR = 2300 ms, and a 32×32 acquisition matrix yielding spectra from voxels of 1 ml of tissue[16] (Figure 1). The signal from scalp fat was reduced by outer volume suppression[16]. Water suppression was achieved as described[17,18]. Total MR acquisition time was about 60 minutes.

Data analysis. Processing included 3D-FFT, cosine filtering in k-space, exponential apodization (3 Hz), and zero filling to 1024 points in the time domain. Residual water signals were reduced by a high pass convolution filter. Spectra were selected in lesions and normal appearing periventricular white, occipital white, and occipital grey matter identified on the T2 weighted images (Figures 2, 3), reducing effects from anatomic variations in metabolite concentrations. Spectra were integrated to determine the area for NAA (1.9–2.1 ppm), creatine (Cre) (2.9–3.1), choline (Cho) (3.1–3.3), and lactate (Lac) (1.1–1.4) peaks. The resulting metabolite values were expressed as the ratios NAA/Cre, Cho/Cre, and Lac/Cre. Values from 5 adjacent voxels in each anatomic region were averaged for each metabolite.

The mean coefficient of variation for the scanning procedure was 3.2% for NAA/Cre and 6.6% for Cre/Cho, and for the analysis method for NAA/Cre was 3.5% and for Cre/Cho 4.4%. Means of nonpaired data were compared using 2 tailed t tests, and paired data were compared using paired difference t tests (corrected for multiple comparisons).

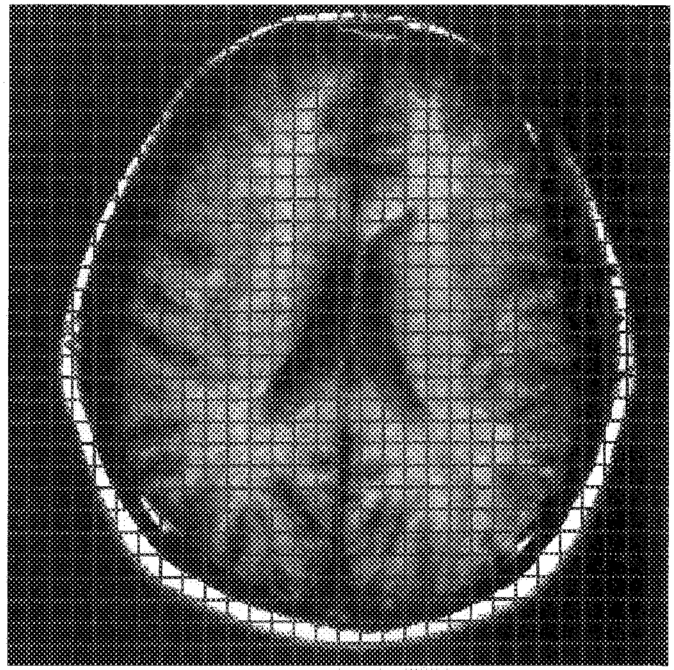

Figure 1. Spectroscopic imaging grid shown here superimposed on a T1 weighted image. Individual cells in the grid provide individual MR spectra, each of which corresponds to anatomic volumes of interest (voxels) 1 ml in volume on the MR image.

RESULTS

Figure 2 shows a typical proton MR image and SI spectra from periventricular white matter, occipital white matter, and occipital grey matter of a healthy control. Mean NAA/Cre and Cho/Cre were higher in normal white matter compared to grey matter ($p < 0.05$). Figure 3 (voxels A and B correspond to white and grey matter, respectively) is the image and spectra of a patient with SLE with extensive white matter lesions. NAA/Cre is lower throughout the brain, but particularly reduced in lesions. In Figure 3, the voxels labeled C and D reveal markedly different spectra in lesions that appear similar by MRI.

Tables 2–4 summarize the results of the study. NAA/Cre was lower in patients with SLE in all regions of brain ($p < 0.05$) (Table 2). No significant differences in mean NAA/Cre were noted in normal appearing white matter between those patients with or without lesions (Table 3). A paired comparison of lesions with normal appearing brain in the same anatomic location from the contralateral hemisphere in individual patients showed a reduction of NAA/Cre in lesions ($p < 0.05$) (Table 4).

Mean Cho/Cre of normal appearing white matter in SLE was not significantly different from controls ($p > 0.05$) (Table 2). However, normal appearing tissue of 21% (4/14) of patients with SLE and 25% (4/16) of focal lesions revealed increased Cho/Cre compared with normal values (mean of control Cho/Cre + 2 SD). Cho/Cre in normal appearing tissue of patients with fixed focal lesions was elevated compared to patients with SLE without lesions (Table 3).

No increase in Lac/Cre was observed in either lesions or normal appearing tissue in patients with SLE compared to controls ($p > 0.05$). Patients treated with corticosteroids or not receiving corticosteroids showed no significant differences in neurometabolites ($p > 0.5$).

DISCUSSION

NPSLE is a serious complication of SLE that remains difficult to diagnose and treat. MRI has greater sensitivity than computed tomography (CT), single photon emission com-

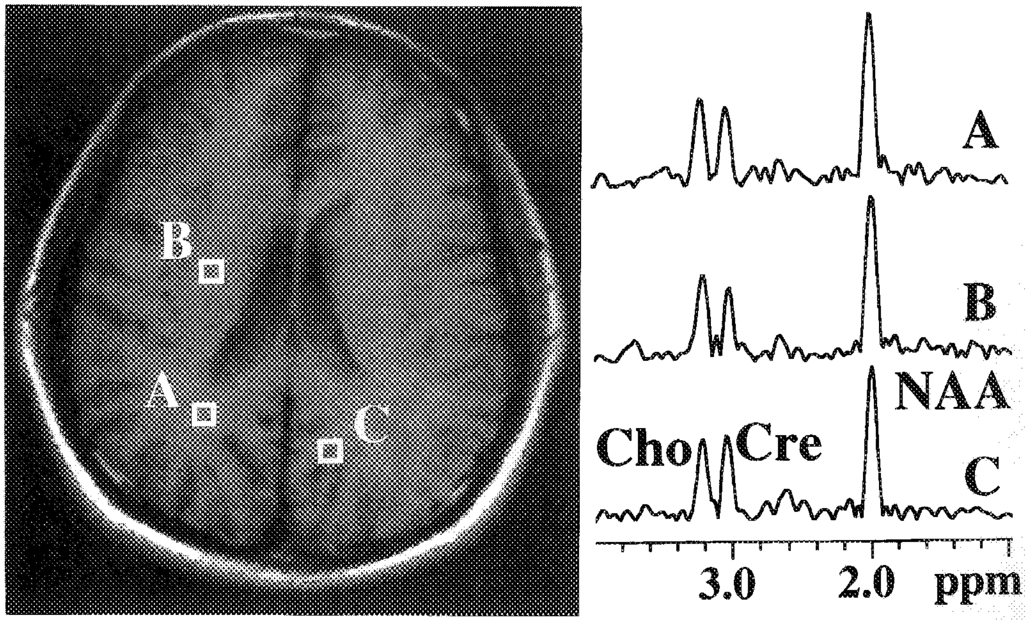

Figure 2. T1 weighted image of a healthy control showing locations of spectral voxels in (A) occipital white matter, (B) periventricular white matter, and (C) occipital grey matter. Right: Spectra from voxels A, B, and C, showing the expected lower levels of NAA relative to Cre in grey matter (C).

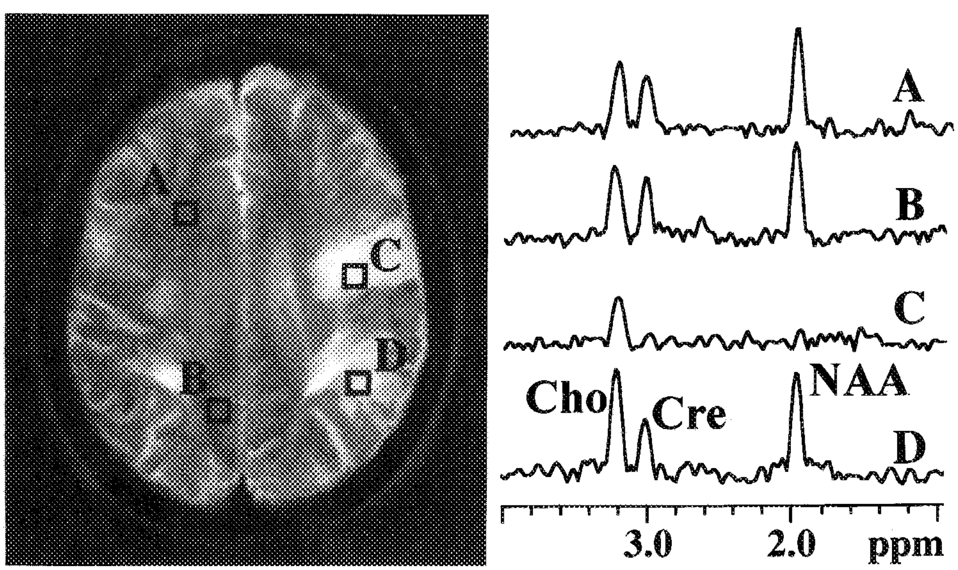

Figure 3. T2 weighted image of patient with NPSLE with multiple lesions showing the locations of spectroscopic voxels. (A) normal appearing white, (B) normal appearing grey, (C and D) hyperintense lesions. Right: Spectra from voxels A, B, C, and D, showing decreased NAA and increased Cho. These abnormalities are accentuated in the lesions (C and D) that show different spectroscopic patterns relative to NAA, Cre, and Cho, indicating considerable metabolic heterogeneity within the population of focal lesions.

Table 1. Patient data for the NPSLE subject group.

Patient	Age, Sex	SLEDAI	Current Prednisone Dose (mg/day)	Previous Major NPSLE Symptoms (yrs elapsed)	Current NPSLE Symptoms	MRI Findings
1	60 M	20	20	Strokes (1.5)	Memory deficits	Atrophy, multiple infarcts, punctate lesions
2	46 F	10	0	Strokes (5)	Memory deficits	Atrophy, infarct, punctate lesions
3	46 F	30	15	Strokes (2)	Expressive aphasia	Multiple infarcts, punctate lesions, atrophy
4	36 F	25	0	Cognitive dysfunction (7)	Dementia, headache	White matter changes, punctate lesions, atrophy
5	36 F	20	10	Depression (2)	Fatigue, headache	Punctate lesions, mild atrophy
6	24 F	25	0	Depression (1)	Fatigue, depression	Normal
7	37 F	5	0	None	Fatigue	Normal
8	40 F	10	0	None	Headache, memory deficits	Normal
9	43 F	14	5	Seizures (3)	None	Few punctate lesions, mild atrophy
10	38 F	18	10	None	Headache	Normal
11	33 F	10	10	None	Headache, memory deficits	Few punctate lesions
12	20 M	5	0	Seizures (3)	None	Few punctate lesions
13	42 F	10	0	None	Headache, memory deficits	Few punctate lesions, moderate atrophy
14	48 F	25	10	Depression, headache (1)	Fatigue, memory deficits	Few punctate lesions, atrophy

SLEDAI: SLE Disease Activity Index.

Table 2. Proton MR spectroscopic imaging in controls and patients with SLE. "SLE" indicates normal appearing brain (nonlesional tissue) by MRI in patients with SLE who may or may not have MRI visible brain lesions elsewhere. This analysis was performed with the 2 tailed t test.

Metabolite Ratio–Brain Region	Control (n = 13) Mean ± SD	SLE (n = 14) Mean ± SD (p)
NAA/Cre–Occipital grey	1.92 ± 0.18	1.74 ± 0.16 (0.01)
NAA/Cre–Occipital white	2.23 ± 0.16	1.98 ± 0.22 (0.004)
NAA/Cre–Periventricular white	2.33 ± 0.23	2.00 ± 0.22 (0.001)
Cho/Cre–Occipital grey	0.93 ± 0.10	0.94 ± 0.12 (0.72)
Cho/Cre–Occipital white	1.17 ± 0.19	1.27 ± 0.32 (0.36)
Cho/Cre–Periventricular white	1.30 ± 0.19	1.33 ± 0.21 (0.74)

Table 3. Proton MR spectroscopic imaging of normal appearing tissues in patients with SLE with and without focal lesions. This analysis was performed with the 2 tailed t test. These comparisons represent normal appearing brain tissues from patients with SLE with and without fixed focal lesions.

Metabolite–Brain Region	SLE without lesion (n = 8) Mean ± SD	SLE with lesion (n = 6) Mean ± SD (p)
NAA/Cre–Occipital grey	1.75 ± 0.14	1.72 ± 0.19 (0.73)
NAA/Cre–Occipital white	2.05 ± 0.23	1.90 ± 0.20 (0.22)
NAA/Cre–Periventricular white	2.04 ± 0.24	1.94 ± 0.21 (0.40)
Cho/Cre–Occipital grey	0.88 ± 0.07	1.03 ± 0.14 (0.02)
Cho/Cre–Occipital white	1.13 ± 0.13	1.46 ± 0.41 (0.06)
Cho/Cre–Periventricular white	1.22 ± 0.11	1.46 ± 0.19 (0.02)

Table 4. Comparison of focal lesions with normal appearing brain in individual patients with SLE. Lesional tissue was anatomically matched with normal appearing nonlesional tissue on the contralateral side of brain of the same individual patient with SLE and compared by paired t test.

Metabolite Ratio	Focal Lesion in SLE Patient (n = 16) Mean ± SD	Normal Brain in Same Patient (n = 16) Mean ± SD (p)
NAA/Cre	1.67 ± 0.23	1.88 ± 0.14 (0.0002)
Cho/Cre	1.54 ± 0.31	1.56 ± 0.17 (0.74)

puted tomography (SPECT), and positron emission tomography (PET) for detecting focal brain lesions in NPSLE, and is the method of choice for evaluating brain anatomy of patients with SLE[6,9,19]. Focal lesions typically appear as high intensity foci in white matter on T2 weighted MR images. Reversible lesions may represent focal demyelination or cerebral edema associated with seizures or blood–brain barrier breakdown[9]. Large, fixed focal lesions usually represent stroke and are visible by both CT and MRI[7,9].

Smaller fixed focal lesions evident on T2 weighted MR images may represent small infarcts in subcortical or deep white matter[10,20–22]. Although focal hyperintense lesions appear similar to each other on MR images, they may be of different etiology, age, and significance. The concept of heterogeneity of lesions in NPSLE is supported by our finding of different relaxation properties in focal lesions, indicating different microenvironments, histopathology, and neurochemistry[13]. It is difficult to reconcile the presence of fixed focal lesions with reversible neurologic manifestations[23,24]; however, normal aging populations do show hyperintensities not associated with clinical deterioration[25]. It may be that the reversibility of functional disturbances in SLE does not necessarily indicate reversible neuronal injury, in that the brain may accommodate considerable neuronal injury yet maintain normal or near normal function. However, if the neurochemistry of fixed focal lesions were consistent with neuronal injury, then it could be inferred that white matter lesions in NPSLE represent a serious pathologic process resulting in focal neuronal death or injury[26].

Magnetic resonance spectroscopy (MRS) has permitted determinations of the neurochemistry of NPSLE[11,12,27–29]. Metabolites measured by MRS include N-acetylaspartate, choline-containing compounds, creatine + phosphocreatine, and lactate. NAA is the strongest peak in a normal adult [^{1}H]MR brain spectrum, and is generally regarded as a specific chemical marker for neurons[30,31]. NAA is reduced in stroke, multiple sclerosis, and schizophrenia, disorders associated with neuronal loss, cognitive dysfunction, and cerebral atrophy[32–35]. Cre represents total intracellular creatine and is commonly used as an internal standard. Cho may be elevated due to catabolism of cell membrane components, including myelin[32]. Although the concentration of lactate in resting normal brain tissues is usually undetectable by MRS *in vivo,* lactate is often observed in ischemic tissue, particularly in acute stroke secondary to anaerobic metabolism[31]. Brain lactate levels may also be elevated in the subacute stages of stroke due to inflammatory cell infiltration[36].

We observed that NAA/Cre is markedly reduced in fixed focal lesions relative to normal appearing brain, indicating localized neuronal injury. NAA/Cre is also decreased in normal appearing grey and white matter in NPSLE. These findings indicate both focal and generalized neuronal injury with considerable heterogeneity between individual lesions and individual patients[26]. We have reported that NAA/Cre is decreased in NPSLE patients with cerebral atrophy, suggesting a significant loss of neurons[12]. Reduced NAA suggests severe brain injury, degeneration, or death of neurons[26,36] or possible reversible neuronal injury[37]. While it is likely that the focal lesions characterized by decreased NAA represent the consequences of acute events, the dynamics and clinical associations of NAA loss in NPSLE remain to be determined. Our data indicate that NPSLE is a complex multifocal and diffuse neurotoxic process resulting in severe brain injury with loss of specific neuronal markers. Prospective, longterm studies of NPSLE are required to determine the relationship of NAA to specific neurologic events or systemic disease activity.

Certain white matter lesions were found to have elevated Cho/Cre as well as decreased NAA/Cre. The great variability of NAA/Cre and Cho/Cre in lesions that were anatomically similar indicates a significant population heterogeneity, presumably related to different histology, origin, activity, or age of lesions. Elevated Cho/Cre was also seen in normal appearing tissue in 21% of patients with NPSLE. Choline may be elevated due to breakdown of cellular membranes, catabolism of myelin, or inflammation[32,38]. Similar focal lesions in the elderly are characterized by decreased NAA and increased lactate, but increased choline is not frequently observed, suggesting a different pathologic process in patients with NPSLE[39]. Reduced NAA/Cre and increased Cho/Cre in NPSLE are consistent with foci of neuronal injury, ischemic necrosis, or cellular inflammation of variable extent and stages of temporal evolution[40,41].

Using absolute quantification of metabolite concentration from single voxel spectroscopy, Davies, *et al* have shown that in multiple sclerosis, the concentration of creatine falls[42]. However, our observation that NAA/Cre is decreased while Cho/Cre is increased suggests that changes in Cre are not the primary cause. Indeed, if Cre were decreased, our finding of decreased NAA/Cre indicates an even more dramatic reduction in absolute NAA concentration, suggesting even greater cerebral injury.

Since lactate is elevated in acute stroke, it might be expected that lactate would be increased in stroke-like lesions associated with SLE[7,43]. Although cerebral blood flow studies suggest ischemia in NPSLE[44], we found no elevation of lactate in lesional or normal appearing tissues, indicating the absence of anaerobic metabolism[45]. However, patients with active NPSLE, including those with acute stroke, were specifically excluded in our study design; therefore, the absence of lactate may be due to the nonacute nature of the focal lesions[28]. Alternatively, the concentration of lactate may have been below the detection threshold ($\approx$1–2 mM) of MRS[46].

As shown in Table 1, patients were studied at least one year after their most recent episode of active NPSLE. Thus, the neuroimaging findings were the result of well resolved, rather than recent injury. Half of our patients were being treated with corticosteroids at the time of study (Table 1). Although the effect of steroids on the central nervous system is generally considered to be protective, the effects on neurometabolites remain to be elucidated. In our data set, we found no difference between neurometabolites in patients who had been treated with prednisone and those who had not.

Our previous studies have indicated that fixed and reversible lesions in NPSLE have different relaxation properties[13], and it is likely that fixed or reversible lesions express different metabolic profiles as well. Although the neurochemistry of fixed focal lesions and normal appearing brain in patients with previous NPSLE is consistent with neuronal injury, demyelination, and the lack of anaerobic metabolism, the neurochemistry of fulminantly active NPSLE may be quite different.

SI is a powerful technique that permits the simultaneous neurometabolic analysis of individual lesions and multiple cerebral tissues in patients with NPSLE. Fixed focal cerebral lesions in NPSLE are characterized by loss of the neuronal marker of NAA and increased choline, indicative of focal neuronal loss, demyelination, and inflammation. Certain patients have widespread pathologic changes in normal appearing grey and white matter, indicating a previously unsuspected generalized disorder, most likely widespread microlesions or diffuse neuronal loss. Lactate production is not a characteristic of fixed focal lesions in NPSLE. The temporal evolution of focal lesions, their relationship to active NPSLE, and association with cognitive dysfunction remain to be determined.

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